The Resolution of 2-Hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-Oxide (Phencyphos) by Preferential Crystallization

Leeman, Michel; Querniard, Florian; Kaptein, Bernard; Kellogg, Richard M.

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The Resolution of 2-Hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinan 2-oxide (Phencyphos) by Preferential Crystallization.

Michel Leeman, Florian Querniard, Bernard Kaptein and Richard M. Kellogg

Methods

Materials

All chemicals were obtained form commercial sources and used without further purification.

General Information

Chiral HPLC analysis of phencyphos was carried out on a Chiralpak QN-AX column with MeOH:AcOH 97:3 + 0.25g NH_4OAc/100 mL as mobile phase at room temperature and 1.5 mL·min^{-1}. UV-vis detection was performed at 254 nm. The phencyphos was dissolved in MeOH and injected as such. (+)-*(S)*-phencyphos R_f: 7.34 min, (–)-*(R)*-phencyphos R_f: 8.44 min.
IR spectra were recorded on a Thermo Nicolet 380 FT-IR with Smart Orbit.

Procedure for the construction of the ternary phase diagrams

Just enough (±)-phencyphos·0.84H_2O to achieve a suspension, was slurried in known mixtures of water and DMSO, DMF or MeOH for a couple of days at 20°C. After removal of the solid phase the composition of the mother liquor was determined by weighing the weight loss after evaporation of the solvents *in vacuo*.

Determination of the IR spectra of (±)-phencyphos

Solvates of (±)-phencyphos with either MeOH, EtOH or IPA should give different IR signatures. (±)-phencyphos was recrystallized from these solvents and the solids were analyzed by FT-IR. However, the signatures were similar which indicates that MeOH, EtOH and IPA do not give solvates with (±)-phencyphos as depicted in Figure 1. The recrystallization of (±)-phencyphos from water delivered the monohydrate which, indeed, has a different spectrum (best visible between 1050 and 1250 cm^{-1}) than the (±)-phencyphos recrystallized from MeOH, EtOH or IPA.

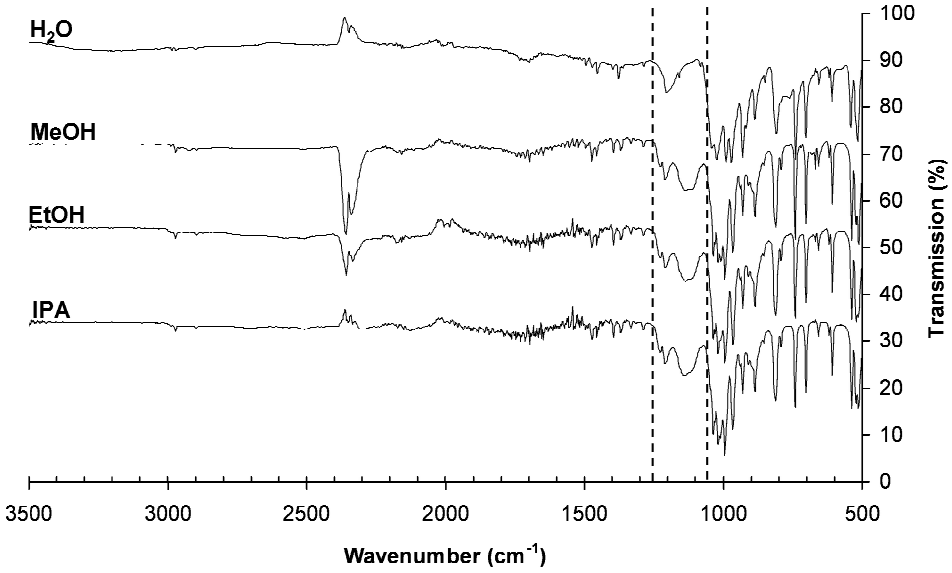

Figure 1 *IR spectra from (±)-phencyphos crystallized from several solvents. The peaks at 2350 cm^{-1} are from CO_2.*

Determination of the solubility of (±)-phencyphos

The solubility of (±)-phencyphos in several pure solvents as described in the main article was performed in a similar fashion to the procedure described above for the ternary phase diagrams and the results are given in Table 1.

Table 1 *Solubilities of (±)-phencyphos in several water miscible solvents.*

Entry	Solvent	Solubility (mg (±)-phencyphos/mL solvent)
1	MeCN	< 1
2	1,4-dioxane	1.1
3	water	3.2
4	ethylene glycol	4.0
5	acetic acid	4.8
6	1-butanol	5.7
7	sec-butanol	5.8
8	IPA	8.4
9	MeOH	17
10	DMF	81
11	DMSO	142

Procedure for the preferential crystallization of phencyphos hydrate on 35L scale

A temperature controlled (Huber Unistat 510) 40L double jacketed glass reactor was charged with (±)-phencyphos·0.84H_2O (861 g, 3.35 mol, 1.0 eq), water (9.25 L) and MeOH (27.75 L) and stirred with a propeller shaped stirrer at 300 rpm throughout the preferential crystallization.

The mixture was biased with (–)-phencyphos hydrate (137 g, 0.52 mol, 0.16 eq) and a temperature program was run where the internal temperature was heated from 28.9°C to 54.0°C as fast as possible (41 minutes) and kept at this temperature for another 5 minutes. Complete dissolution was observed. Then the mixture was cooled to 28.9°C as fast as possible (44 minutes) and kept at this temperature for another 37 minutes. Then the temperature program was repeated. The temperature profile is depicted in Figure 2.

The solids were collected (P2) 10 minutes prior to the reheating to 54.0°C. The filter cakes were sucked dry but not washed. Chiral HPLC analyses (as described above) on the solids were carried out. If the solids had an *ee* greater than 85%, (±)-phencyphos·H_2O (270 g, 1.04 mol, 0.31 eq) was added to the filtrate. If the collected solids had 0% *ee* anhydrous phencyphos was isolated and thus, more water was added and the preferential crystallization repeated by reintroducing the filter cake in the reactor. If the collected solids had an *ee* between 30% and 85%, the concentration of the undesired enantiomer was too high and the preferential crystallization was repeated with the filter cake and replacing some filtrate by MeOH. In a typical run, solids were collected with an average *ee* of 93%. Combined enriched batches were heated and subsequently cooled in a mixture of 30% wt. H_2O in MeOH to give crystals with >99% ee after filtration. In practice the whole resolution process yielded 41% of each enantiomer of optically pure phencyphos hydrate.

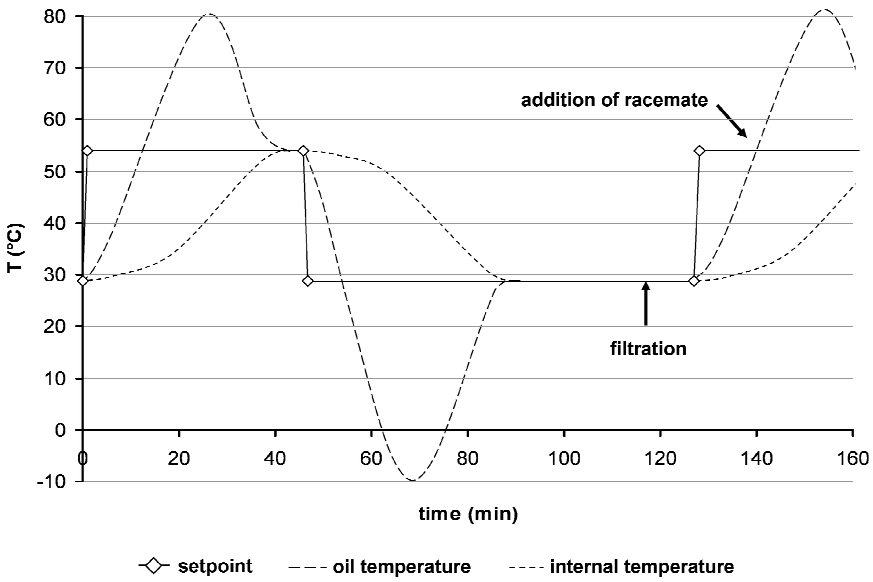

Figure 2 *Temperature program for the resolution by preferential crystallization of phencyphos hydrate on 35L scale. The program repeats itself after 127 min.*